Our Case No. 12346/4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MARY CAPELLI-SCHELLPFEFFER.

Serial No. 09/810,939

Filing Date: March 16, 2001

For METHODS FOR IMPROVING THE SIZE AND APPEARANCE OF A HEALED WOUND

Examiner: Isis Ghali

Group Art Unit No.: 1615

DECLARATION OF RAPHAEL C. LEE, M.D., Sc.D. UNDER 37 C.F.R. § 1.132

I, Raphael C. Lee, M.D. Sc.D., declare that:

1. I received a Masters of Science in 1975 from Drexel Institute of Technology, a Doctorate in Medicine in 1975 from Temple University, and graduated from Massachusetts Institute of Technology in 1980 with a Doctorate in Science in Biomedical Engineering. I completed postgraduate residency training in General Surgery at the University of Chicago in 1981 and in Plastic Surgery at Harvard Medical School (Massachusetts General Hospital) in 1983.

2. I am a Founder and Chairman of Avocet Polymer Technologies, Inc., located at 23560 West Main Street, Plainfield, Il 60544.

3. Avocet Polymer Technologies, Inc. is the assignee of the above-identified application.

4. My scientific Curriculum Vitae is attached to and forms part of this Declaration.

5. I am familiar with acne and acne treatments existing as of 2001.

6. I also am familiar with and have reviewed the above-identified application, including the claims submitted with the Amendment and Request for Continued Examination submitted November 7, 2005, as well as the Office action mailed June 7, 2005 and the references cited therein, including JP-08-268,886 ("JP-886"); DE 27 07 537 ("DE '537"); and U.S. Patent No. 6,521,271 (the "'271 patent").

7. In my understanding, the above-identified application is directed to a novel and inventive method of reducing the size or improving the appearance of a closed wound by administering a composition consisting essentially of a particular non-steroidal anti-inflammatory agent in combination with a pharmaceutically acceptable carrier. I understand that the phrase "closed wound" is defined at page 6 of the specification to refer to an open wound that has been sealed by formation of a new epidermis through the process of re-epithelialization. I also understand that the claims are limited to specific closed wounds that include only wounds caused by mechanical trauma, laceration, avulsion, burn, radiation, chemical facial peel, or accident, wherein a wound resulting from one of these causes leads to a normal scar, a hypertrophic scar, an excessive post-operative scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, or a fibrotic scar.

8. I understand that the Office rejects Claims 80 and 82 as being anticipated by the disclosure of JP-886.

9. I also understand that the Office states that in view of DE '537 and the '271 patent, one of ordinary skill in the art would have known, or it would have been obvious to such a person, to use salicylic acid or aspirin to treat a scar, such as a hypertrophic scar.

10. As one of at least ordinary skill in the art, I disagree with the Office that the invention claimed in the above-identified application is either anticipated or obvious in view of JP -886, DE 537, or the '271 patent. The basis for my opinion that JP-886 does not anticipate the invention claimed in the above-identified application is set forth at paragraphs 11-30 of this declaration. The basis for my opinion that the invention claimed in the above-identified application would not be obvious in view of either DE 537 or the '271 patent is set forth at paragraphs 31-48 of this declaration.

11. I understand that in the Examiner's view, JP-886 "disclose[s] treatment and improvement of the skin diseases such as keloids by administering [a] composition comprising aspirin or its salts in a carrier by external application, orally, or by injection." (Office action mailed 6/7/2005, Pages 4-5).

12. I disagree with the Examiner for at least four reasons. First, JP-886 does not provide any example of a keloid or of a closed wound as that term is used in the claims of the above-identified application. Rather, JP-886 solely discloses administration of satigrel to an *open* punch wound on a rabbit auricle and reports

that such administration suppressed neovascularization. Second, one of ordinary skill in the art would not rely on this solitary example to extrapolate from JP-886 that aspirin might be used to reduce the size and improve the appearance of a *different type of wound*, *e.g.* a closed wound. Third, although JP-886 claims that a large number and wide variety of diseases may be treated by daily oral administration of 0.01-2000 mg of satigrel or aspirin, one of ordinary skill in the art would doubt the truth of such an assertion. Fourth, JP-886 does not provide any guidance for determining what topically administered dosage of aspirin suppresses neovascularization such that a "closed wound" is prevented or treated.

13. JP-886 does not provide any example of treatment of a keloid scar, or for that matter, any type of "closed wound" as that term is used in the claims of the above-identified application. Rather, the only example in JP-886 describes intravenous administration of satigrel to a punch wound on the auricle of a rabbit. More specifically, this example describes that 21 mature domestic rabbits underwent a drum fixation procedure. In particular, in each rabbit, an auricle was shaved and the rabbit was then attached to a metallic drum. The auricle was punched circularly by a puncher. After a punch was made a small-sized scalpel was used to peel the skin off of the outer side surrounding the perimeter of the punch hole. Then, for three weeks, on a once daily basis, satigrel sodium was administered.

14. One of ordinary skill in the art would understand that administration of satigrel on a daily basis, as carried out in the only example in JP-886 (described above),

would prevent the punch and skinless area surrounding the punch from reepithelializing during the three week observation period. Therefore, the only example illustrating any suppression of neovascularization is based on treatment of an *open* wound, *i.e.* a wound that has not reepithelialized.

15. As explained at page 6 of the specification and paragraph 7 of this declaration, within the meaning of the claims in the above-identified application, "[a] wound is 'closed' after an open wound has been re-epithelialized."

16. In my opinion, one of ordinary skill in the art would not rely on the solitary example to extrapolate from JP-886 that aspirin might be used to reduce the size and improve the appearance of a *different type of wound*, *e.g.* a "closed wound."

17. Additionally, one of ordinary skill in the art will appreciate that each disease included within the above-identified wide variety of diseases would be located in different parts of the body and could only be treated with aspirin or salicylic acid by *oral* administration or administration by *injection* into the blood circulation.

18. Indeed, JP-886 suggests that aspirin can be orally administered daily in an amount ranging from 0.01-2000 mg (paragraph 28 of JP-886) to suppress neovascularization and thereby treat or prevent a keloid disease. This use of aspirin is contrary to my experience as a physician during the time period preceding and including 2001.

19. Specifically, as of 2001, one of ordinary skill in the art would know that oral administration of aspirin at doses ranging from 0.01-2000 mg would neither

systemically nor locally suppress neovascularization in an amount sufficient to prevent or treat any of the above-identified diseases. One of ordinary skill in the art also would appreciate that neovascularization is a normal step in the wound healing process and that the aspirin dosage range taught by JP-886 is within the normal, accepted dosage range for oral administration of aspirin. Therefore, if the teaching of JP-886 were true (*i.e.* that oral administration of aspirin at a dosage ranging from 0.01-2000 mg suppresses neovascularization sufficient to treat a keloid), then a person taking aspirin in that normally accepted dosage range for any reason, such as having a headache, would be expected to heal a keloid because allegedly neovascularazation would be suppressed in an amount sufficient to treat a keloid. At the same time, it would be expected that such a person would not be able to heal a wound because wound healing requires neovascularization.

20. However, in my experience as a physician, patients taking aspirin do heal wounds. Further, it is my opinion that one of ordinary skill in the art in 2001 would not have used oral administration of aspirin, in the normally accepted dosage range, as a treatment for a keloid. For example, as described in Example 4 of the above-identified application, described at pages 30-31, a patient suffering from a post-operative scar was taking 325 mg of aspirin per day to prevent thrombo-embolic post-operative complications. Although this patient was being orally administered aspirin on a daily basis, the patient's "closed wound" was neither "treated" nor "prevented" as claimed by JP-886.

21. Thus, the teaching of JP-886 discussed above in paragraph 19 is contrary to the knowledge and understanding that one of ordinary skill in the art would have in 2001.

22. Therefore, in my opinion, as one of at least ordinary skill in the art, JP-886 does not provide any evidence demonstrating that aspirin or any of its salts may be topically administered in an amount ranging from about 0.1 percent to about 10 percent by weight of a pharmaceutically acceptable vehicle to reduce the size or improve the appearance of a wound caused by an external trauma that has reepithelialized, *e.g.* a "closed wound."

23. Indeed, it is my opinion that JP-886 fails to provide any guidance for determining what dosage range might be effective for reducing the size or improving the appearance of a "closed wound." The lack of guidance is significant because as discussed above at paragraphs 18-22, JP-886 only discloses an *oral* dosage range of aspirin. As explained above, one of ordinary skill in the art would appreciate that the oral dosage range disclosed in JP-886 is not sufficient to reduce the size or improve the appearance of a "closed wound."

24. Further, one of ordinary skill in the art also would appreciate that at *high* concentrations, aspirin retards the wound healing process.

25. For example, in the *Journal of Pharmaceutical Science*, K.H. Lee *et al.* describe an injury similar to that discussed in the example set forth in JP-886. Specifically, Lee describes an injury where a circular piece of skin, about 5 cm in diameter, was removed from the back of Sprague-Dawley rats. The wounds

remained undressed. Wound healing was measured by quantification of tensile strength (*i.e.* measurement of the force required to open a healing skin wound). Table I reports that rats receiving an oral dose of 150 mg/Kg of aspirin daily have an average tensile strength of skin wound that is about 60% that of control. Table I further reports that when the dose of aspirin was reduced to 75 mg/Kg, the average tensile strength of skin wound was about 78% that of control. Therefore, Lee concludes that aspirin retards wound healing. *See* Lee, KH. "Studies on the mechanism of action of salicylates. 3. Effect of vitamin A on the wound healing retardation action of aspirin." *J Pharm Sci.* 1968. 57(7):1238-40.

26. In a related article, KH Lee *et al.* report that approximately 6 cm incisions were made on the backs of Sprague-Dawley male rats. The incisions were allowed to cease bleeding in a normal manner and were sutured using black silk surgical thread. The wounds were left undressed. Fifty mg of sodium salicylate dissolved in a small amount of water was fed to the rats daily for 4 days through a short stomach tube. Again, wound healing was measured by quantification of tensile strength (*i.e.* measurement of the force required to open a healing skin wound) seven days after wounding. In Table II, Lee reports that Group II, which consisted of 8 rats who were orally administered sodium salicylate, exhibited a mean tensile strength that was only 79% that of the control group of rats. Similarly, Table II reports that in Group IV, which consisted of 11 rats who were topically administered 3% salicylic acid in a non-ionic base, the mean tensile strength was only 88% that of the control group. K.H. Lee *et al.* conclude that this study shows retardation of wound healing by aspirin. *See* Lee, KH *et al.*,

"Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." *J Pharm Sci.* 1968. 57(6):1042-3.

27. Further, in my opinion, one of ordinary skill in the art would doubt the claim in JP-886 that the large number and variety of diseases described therein could be treated or prevented by administering satigrel or aspirin. In particular, in the one example described in JP-886, discussed above at paragraph 13, it is reported that angiogenesis was suppressed when satigrel sodium was administered. Based on this example, JP-886 claims that "it was shown that it can become prevention treatment improving agents for stomach cancer, a lung cancer, a hepatic carcinoma, a colon cancer, a rectal cancer, a pancreatic cancer, a prostatic cancer, a bladder cancer, a renal cancer, an ovarian tumor, a uterine cancer, a breast cancer, skin cancer, malignant melanoma or a basal cell carcinoma, keloid, inflammation, diabetic retinopathy, *etc.*" (Paragraph 39 of JP-886).

28. It is my opinion that one of ordinary skill in the art would not rely on the teachings of JP-886 because such a person would doubt that satigrel or its salts, aspirin or its salts, or some combination thereof can be used to treat or prevent the enormous variety of diseases claimed to be treated or prevented in JP-886.

29. In particular, in my view, one of ordinary skill in the art would be very skeptical of JP-886 because the reference fails to provide any example that demonstrates treatment or prevention of any of the above-identified diseases.

30. Therefore, in my opinion, JP-886 does not enable one of ordinary skill in the art to conclude that topically administering aspirin or any of its salts in an amount ranging from about 0.1 to about 10 percent by weight of a pharmaceutically acceptable carrier will reduce the size or improve the appearance of a "closed wound".

31. Turning now to DE 537 and the '271 patent, according to the Office action mailed June 7, 2005, DE 537 states that salicylic acid may be used in a thixotropic gel for the "local treatment or control of hypertrophic cicatrisation in acne." (Office action mailed 6/7/05, Page 5). DE 537 explains that the preparation described therein "serves for the treatment of sebaceous accumulations, pustules, and papules, as they may occur in Acne vulgaris" and "is also suitable for the treatment of tinea versicolor, seborrheic dermatitis, as well as other disorders, which are associated with hyperplasia that has been brought about by infected sebaceous glands." (Office action mailed 6/7/05, Page 7).

32. The '271 patent states that "compositions comprising at least one of the components of turmeric (such as curcumin or turmerin) and alpha hydroxy acid . . . promote improvement of skin condition." (col. 3, ll. 8-11). The '271 patent further states that "when combined with alpha hydroxy acid, the component(s) of turmeric (in particular curcumin and turmerin) are able to penetrate the skin and have a pronounced effect on the skin being treated that would not be achieved in the absence of alpha hydroxy acid." (col. 4, ll. 41-45). The '271 patent also teaches that salicylic acid may be used in the compositions described in that patent. According to the '271 patent "Salicylic Acid (Beta Hydroxy Acid) has

been shown to aid in dead skin removal . . . and to have a keratoloytic effect that is useful for skin treatment." (col. 9, ll. 4-9).

33. I disagree that in view of the DE 537 reference and the '271 patent one of ordinary skill in the art in 2001 would have used salicylic acid to treat the types of external wounds and scars to which the invention of the present application is directed.

34. My disagreement is based at least in part on the etiology of acne and the mode of action of salicylic acid in acne treatments. It is commonly known and widely accepted that acne forms inside a skin pore as a result of abnormal desquamation of cells of the follicular epithelium. More specifically, a skin pore is an opening in the skin through which a very fine hair typically will grow and sweat glands will drain. Skin pores are connected to sebaceous glands, which produce an oily sebum that lubricates the hair and skin. Acne occurs when the sebaceous glands produce thick highly viscous oil that when combined with the desquamated cells, forms a plug that obstructs further drainage of sebum. This results in an enlarged, blocked pore called a comedo. Plugged pores create a breeding ground for skin bacteria. As the bacteria flourish in the comedo, skin infection begins leading to pain, inflammation, and scarring.

35. Existing acne treatments focus on *slowing* down the skin's production of oil, and *encouraging* rapid desquamation (*e.g.* shedding of dead skin cells), or *fighting* bacteria. Increasing desquamation leads to larger diameter skin pores and thinner epidermis and better drainage of the pore.

36. More specifically, salicylic acid is lipid soluble, which means it can penetrate into a pore containing sebum and loosen desquamated skin cells built up inside the pore. Indeed, it is well *understood and widely accepted in the art that salicylic acid treats acne by loosening the intercellular cement material present in the pores, increasing the diameter of the skin pore, and by thinning the epidermis, which drains the plugged pores and prevents further plugs from forming. By draining the skin pores and removing the infection, inflammation and fibrous tissue formation are reduced. Thus, any treatment that would cure acne would also indirectly prevent acne scaring. See e.g.*, Davies, M. and Marks, R. "Studies on the effect of salicylic acid on normal skin." *Br. J. Dermatol.* 1976. 95(2):187-92 and Roberts *et al.*, "Detection of the action of salicylic acid on the normal stratum corneum." *Br. J. Dermatol.* 1980. 103(2):191-6.

37. It is my opinion as one of at least ordinary skill in the art that based on the understood mode of action of salicylic acid in acne treatments (discussed above), one of ordinary skill in the art would not expect that salicylic acid could be used to treat either an external wound, including one that has reepithelialized, or a scar caused by an external trauma.

38. Furthermore, it is well known and generally accepted that salicylic acid should not be used on wounds with a weakened external barrier, such as open wounds or wounds that have recently reepithelialized. Further, even after the filing date of the present application, it was believed that use of salicylic acid on inflamed, irritated, or infected areas of the skin can cause severe irritation. *See e.g.*, Rhein *et al.*, "Targeted delivery of salicylic acid from acne treatment products into and

through skin: role of solution and ingredient properties in relationships to irritation." *J. Cosmet Sci.* 2004. 55(1):65-80. *See also* USP DI Advice for the Patient [Internet]. [Greenwood Village (CO)]: Thomson MICROMEDEX; ©2005. Salicylic acid; [revised 2005 Jan 19; cited 2005 October 7]; [~ 8 p.]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202516.html (attached).

39. Therefore, in my opinion, as one of at least ordinary skill in the art, I would expect that salicylic acid would cause severe irritation of the skin if the salicylic acid was administered when the epidermal barrier was weakened or lost, as happens with external wounds. Indeed, one of ordinary skill in the art in 2001 would expect salicylic acid to delay the wound healing process, irritate and exacerbate, not alleviate, scarring in skin tissues that are in recovery from an external trauma.

40. In addition to the above-reasoning, my opinion is based on my understanding of how an injury or wound caused by an external trauma heals.

41. The injury healing process resulting from trauma typically progresses in an orderly sequence over several months to a couple of years.

42. The healing process for a wound caused by an external trauma is typically divided into three distinct phases. The initial phase is generally referred to as the inflammatory phase. This phase occurs immediately following external tissue injury and typically lasts about 5 days. The inflammatory phase involves neutrophil infiltration with subsequent replacement by macrophages and lymphocytes. Neutrophils function primarily to clean the wound environment by production of superoxides that kill bacteria and by phagocytosis of necrotic

material. The major object of this phase is to gain immunologic control of the wound and trigger the wound repair process.

43. During the next phase of wound healing, the transitional repair phase, macrophages produce growth factors and other cytokines which promote fibroblast migration, proliferation, and collagen synthesis. Thus, the density of cells in the tissue around the wound increases and a transitional tissue matrix is formed. New vessels and epithelium are formed as rapidly as possible to maximize the tissue replacement dynamics. Most wound cells are maximally active and are very sensitive to factors that regulate cell growth and tissue matrix synthesis. Also, enzymes are released into the extra-cellular fluid to activate a simultaneous tissue matrix breakdown process. Under normal conditions, this stage begins several days after the injury and lasts several weeks. However, if the inflammatory stage is severe because of severe trauma, infection, or presence of tissue irritants, this phase will persist longer. Prolongation of this phase leads to hypertrophic or keloid scarring.

44. The third and final phase of wound healing, the maturation phase, typically begins approximately 6-12 weeks after wounding. When enough transitional matrix is formed, a turn-off signal is received, and the maturation phase begins. During this phase, cellular apoptosis occurs and there is a shift from scar remodeling toward scar degradation.

45. In my opinion, one of skill in the art would understand that factors that increase or prolong wound inflammation or wound tension predispose an individual to

hypertrophic scar formation. *See e.g.*, Chan, TY. "Potential dangers from topical preparations containing methyl salicylate." *Hum. Exp. Toxicol.* 1996, 15(9):747-50 and Tanveer Ahamed Kahn, "A preliminary investigation of chitosan film as dressing for punch biopsy wounds in rats." *J. Pharm Pharmaceut Sci.* 2003, 6(1):20-26 (skin irritation effect of a compound compromises its use as a wound dressing, p. 26).

46. Additionally, in my opinion, one of ordinary skill in the art would understand that during the initial phases of wound healing, the newly forming epidermis covering and surrounding the wounded area is extremely thin and sensitive and susceptible to acidic agents such as salicylic acid, which causes desquamation of the epidermis, and irritates the wound. These effects lead to delayed wound healing and prolonged inflammation. *See e.g.*, Lee, KH. "Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." *J Pharm Sci.* 1968 Jun;57(6):1042-3.

47. Therefore, it is my opinion that in 2001, a skilled artisan would not treat a "closed wound," particularly during the inflammatory and early transitional repair phases, with a treatment such as salicylic acid, which is known to delay the wound healing and cause severe irritation when applied to inflamed sensitive skin.

48. Neither the DE 537 reference nor the '271 patent provides motivation for one of skill in the art to use salicylic acid *by itself* to improve the appearance or reduce the size of a wound caused by an external trauma. Thus, for the reasons discussed above, I disagree with the Examiner.

49. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on knowledge and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements, and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of the patent application or any patent issuing thereon.

12/22/05
Date

Raphael C. Lee, M.D., Sc. D.